

The paragraphs on pages 10-18 disclosing the nucleotide sequences of the Z-chromosome specific markers recited in claim 1 and the listing of the sequences in claim 1 are amended to identify the SEQ ID NOs of the respective sequences as called for in the Office Action dated March 9, 2002.

No new matter has been added by way of the newly submitted claims.

Claims 1-9 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter that was allegedly not enabled by the specification. The Office Action of March 9, 2002, summarized the *Wands* factors that are considered in determining whether the description of an invention in a specification enables one skilled in the art to use the invention without having to perform undue experimentation (*In re Wands*, 8 USPQ2d 1400, Fed. Cir. 1988), and concluded that undue experimentation would be required to use the claimed invention. The Office Action seems to take the position that the specification must disclose how the present invention can be used to detect "any and all deletions, translocations, or insertions" of avian Z chromosomes, or describe chromosomal rearrangements associated with specific disease states or physiological conditions, and must also disclose a genetic map that relates the disclosed Z-chromosomal marker sequences to one or more DNA sequences encoding known proteins, in order to enable one skilled in the art to use the invention without undue experimentation (see page 7).

The Applicants respectfully traverse the position that undue experimentation is required for one skilled in the art to use the claimed invention. The specification discloses the nucleotide sequences of the claimed Z-chromosomal DNAs, and it describes practical ways in which the claimed DNAs can be used, e.g., for specifically labeling avian Z chromosomes to detect gross chromosomal rearrangements, and for genotyping individuals an avian population by detecting Z-chromosomal polymorphisms at multiple loci in the Z chromosomes of individuals in an avian population. Those skilled in the art recognize that detectable nucleic acid hybridization probes that specifically hybridize to a single chromosome are useful for identifying the target chromosome in a preparation containing a number of different chromosomes. As taught on of the textbook, *The Molecular Biology of the Cell*, the display of metaphase chromosomes at mitosis is called a "karyotype," and gross chromosomal rearrangements such as deletion or translocation can be detected by visually

observing changes in the shapes of chromosomes that are labeled with detectable, chromosome-specific hybridization probes (see page 199 of Alberts et al., 4th Edition, Garland Science, NY, 2002, copy attached). The description of chromosome "painting" with labeled hybridization probes that hybridize specifically to single chromosomes in the Alberts et al. textbook is illustrated in Fig. 4-10 on page 199 with photos of fluorescently labeled chromosomes from a 1996 Science article by Schrock et al. (Science, 273:494-497). Pages 6-8 of the present specification teach that the DNA sequences recited in claim 1 specifically hybridize under highly stringent conditions to both chicken and turkey Z chromosomes, and that they can be labeled to fluoresce and hybridized under stringent conditions to avian metaphase Z chromosomes in a fluorescent in situ hybridization (FISH) assay to detect gross chromosomal rearrangements. The applicants respectfully submit that the description in the Alberts et al. textbook of using labeled hybridization probes that hybridize specifically to individual chromosomes in order to detect gross chromosomal rearrangements is evidence that one skilled in the art would reasonably have understood how to use the claimed DNAs of the present invention without undue experimentation.

The Applicants further submit that it is improper to require that the specification disclose a genetic map that relates the disclosed Z-chromosomal marker sequences to one or more DNA sequences encoding known proteins in order to enable one skilled in the art to use the invention without undue experimentation. Pages 9-10 of the specification describe a working example in which PCR primers that specifically hybridize under stringent conditions to chicken Z chromosomal sequences listed in claim 1, or to their complements, were used to specifically amplify 14 different Z chromosomal loci that are polymorphic in an arbitrarily selected avian population (the East Lansing Reference Population - see page 9, line 16). Those skilled in the art of avian breeding would appreciate that the specification describes using the claimed DNAs to detect polymorphisms at defined genetic loci in Z chromosomes of individuals in a population, and would recognize that the specification discloses a new, rapid, and efficient method for genotyping of individuals in an avian population. Those in the art of avian breeding recognize that an assay that permits rapid and efficient genotyping of individuals in an avian population has substantial, real-world utility. The recombinant DNA and PCR technologies required to use the claimed nucleic acids for genotyping of individuals in an avian population are well-known and routine. Accordingly, the Applicants

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submit that the specification enables one skilled in the art to use the claimed invention, and respectfully request reconsideration and withdrawal of the enablement rejection under 35 U.S.C. §112, first paragraph.

The rejections of claims 2-9 under 35 U.S.C. §§ 101 and 112, first and second paragraphs, are moot, as these claims are cancelled.

Claims 1 and 2 were rejected under 35 U.S.C. § 102(b) as being anticipated by Kim et al., on the grounds that claim 2 could be construed to encompass a genomic library comprising Z chromosomal DNA sequences. Claim 2 is cancelled, and the DNA sequences recited in claim 1 do not also include unrecited DNA molecules. The Applicants therefore respectfully request withdrawal of the rejection of claim 1 under 35 U.S.C. §102 (b).

All issues raised by the Office Action dated March 9, 2002, have been addressed in this Reply. It is respectfully submitted that the present application is in a condition for allowance and a Notice to that effect is earnestly solicited. If the Examiner has any further questions or issues to raise regarding the subject application, it is respectfully requested that he contact the undersigned so that such issues may be addressed expeditiously.

Respectfully submitted,

PILLSBURY WINTHROP LLP

Date: September 9, 2002

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Enclosure

APPENDIX

The text and claims are amended as shown below:

IN THE SPECIFICATION:

The paragraph beginning on line 19 of page 5 is amended as follows:

-- The Z-chromosome-specific DNA fragments were fluorescently labeled by PCR with biotin-l6-dUTP (3:1 ratio of dTTP:biotin-l6-dUTP) and passed through a Sephadex G-50 column to remove unincorporated nucleotides. The protocol described by Ponce de Leon (*Proc. Natl. Acad. Sci., USA* (in press) (1996)) was followed. Briefly, 200 nanograms of labeled Z-chromosome specific DNA was mixed with 6 μ g of chicken competitor DNA (average size 200-400 bp) and 5.8 μ g of salmon sperm DNA (average size 200-400 bp), precipitated and resuspended in 12 μ l of hybridization buffer consisting of 50% deionized formamide, 1X SSC and 100% dextran sulphate to achieve a final DNA concentration of 1 μ g/ μ l. The hybridization mix was denatured at 75°C for 5 minutes and reannealed at 37°C for 10 minutes and deposited on denatured (70% formamide, 2X SSC at 70°C for 2 minutes) chicken or turkey metaphases, mounted, sealed with rubber cement and incubated in a humidified chamber at 37°C for 18 to 20 hours. The slides were washed in 50% formamide/2X SSC at 42°C for 15 minutes and 0.1X SSC at 60°C for 15 minutes. Blocking was done using 2% blocking reagent (Boehringer Mannheim) and the signals were detected using avidin-FITC (5 μ g/ml, Vector labs) in 1% blocking solution. Slides were washed in 4X SSC/0.1% [Tween-20] TWEEN-20 (polyoxyethylene sorbitan monolaureate) for 15 minutes at 42°C, stained for 10 minutes in propidium iodide (400 ng/ml in 2X SSC) and rinsed for 5 minutes in 2X SSC/0.01% [Tween-20] TWEEN-20. Slides were mounted in p-phenylenediamine-11 (PPD-11) antifade and observed under a Zeiss Axioskop fluorescent microscope. --

Please amend the captioned paragraph beginning on line 13 of page 10 as follows:

-- SEQUENCE 1 (43.Seq)

1 gatcactttc cctaatttc ttgttttct tgtttgtga cctgtaatgc
51 agttctgagt ttggaaagg aactaattaa gaccagagga gagataattt
101 tcttttatca aaaaacaaac aaacaaacaa aaaaacgaat tcttaccact
151 ttacaaaaat ttccatttt gaaggccagt acagccatag cattcatcta
201 ctttttgctt tggat (SEQ ID NO: 1) --

Please amend the captioned paragraph beginning on line 1 of page 11 as follows:

-- SEQUENCE 2 (71.Seq)

1 gatcaggtgg cctgtagtag acaacaacaa caatgggggtg ccctttgttg
51 ccttagtcct taactegcac ccacacacac ttcaagttg ctgtggcca
101 ttcttcaggg acagttcttc acaatctatt cctttctga tgtagaaggc
151 gtcacctct cccctctgc ctggttgc cttctaac tgcaggtatt
201 agtattgata gctaaggta agtcatggga accatctcac caggttcag
251 tgttggaac tatgttatgc ttcttagga gcatggtggt tccaactctt
301 ccctgcttat ttccaagct gtgtgtgatg gtaggatagc attcaagtgg
351 gaggagccta tcggctttt ggaggtactc ctaaaccct gatattcccc
401 tgattcccg acttcttct tgccaagggc ccgccaatgc atagttcaat
451 ttctcatgca gacgctaagg aaaggtggac cc (SEQ ID NO: 2) --

Please amend the captioned paragraph beginning on line 12 of page 11 as follows:

-- SEQUENCE 3 (80.Seq)

1 gatcgtatgt atttttttac ataggataga aaatggccaa taggaaataa
51 gacagtacag ctactaagaa agaaacacaa ttacacacac acacacacac
101 acacacacac acacatttga aaaacgcgct gcacagcagt gtgggtattt
151 ttccacaaga gagacacact ctacagtaca cagccagctc tactttgtcg
201 cacagtctca gtgtgtgttt gccaacagga cgcggttcac agggagatat
251 tgtcctcttg tgtgtgtgga gacacagaga cagag (SEQ ID NO: 3) --

Please amend the captioned paragraph beginning on line 1 of page 12 as follows:

-- SEQUENCE 4 (81.Seq)

1 gatcccttgg aggaaggga atggcaacc actccagtat tcttcctga
51 agaataccat ggtcagtttt gcctcctggg ctatagtcca tggggttgca
101 aagagtcagg catgactgag cgactctctc tctctctctc tctctctc
151 acacacacac acacacacac acacacggcg tctctctctc tctctataca
201 tataggctgt gtgtctcgt attctcatat gagggaaact catatctagc
251 acgtggcaca aatattgttt gtggctctca caaaagacat gtgggcgcac
301 aaagggtccc ccccggtgga tacanccct tggttttta taaccaagc
351 ctgtg (SEQ ID NO: 4) --

Please amend the captioned paragraph beginning on line 10 of page 12 as follows:

-- SEQUENCE 5 (131.Seq)

1 gatcacatat gtaaactagg gaattgcata ataagattaa atgtaggtgt
51 agaacgtggc atgaaggaag gtagaattag gtggtaccta tctctctga
101 aacaaactga gaatcctact accaatcaac atattctaca taccacacac
151 acatttttc tcgagtaaaa tataaactaa tgagaaactt ccctag (SEQ ID NO: 5)

Please amend the captioned paragraph beginning on line 15 of page 12 as follows:

-- **SEQUENCE 6 (147.Seq)**

1 gatcccaagc aacacatagn cagacaatca cacacacaca cacacacaca
51 cacacacaca cacacacaca cacatcctct ccccaacaata catcccgaga
101 ggggggagag acactctctc tcctctctta taggggagac ccggagagct
151 ggctctgttg tctctctaca ccggacatac agtggagcac atctcacact
201 tgtgtctttg tctctctaca ccggacatac agtggagcac atctcacact
251 tgtgtctcta tctctcctg tcctgttga tccatctctc ttcacacatc
301 tctccagatc tttagcctag agtctctgt cttctctctg cgcaattgt
351 gtgatagaga cacctgatat gttgtgtggg ggagacatct gtgtgtctct
401 gtgtcatccc agaggatttt tctctccac acttagaggc cttctcaaga
451 gatgggaggt ttaatgggg tgtg (SEQ ID NO: 6) --

Please amend the captioned paragraph beginning on line 6 of page 13 as follows:

-- **SEQUENCE 7 (166.Seq)**

1 gatcattctt ctgtttccca ttctaattggg aattctccac acacacacac
51 acacacacac acacacacat cttcttcccc ttacatggaa aaaaatcctc
101 cacaccctg gacactgatt actctccctc tcccagaga gagatc (SEQ ID NO: 7) --

Please amend the captioned paragraph beginning on line 10 of page 13 as follows:

-- **SEQUENCE 8 (196.Seq)**

1 gatcccctag agaagggaat ggctactcac tccagtattc ttgcctggag
51 aattccgtgg tcagaggagc ctggaaggct ataatccata gagtcgcaag

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101 agtcagacag gactgagtga ctaacacaca catgcacaca cacacacaca
151 cacacacaca cttgctctag ggagaggcat agagatgtaa tctctcctaa
201 aatgggggtg gcgatggccc ctgcggccaa gtaatcgcca cacatgcgta
251 ttccccctaa gattgggtta ggccctccctt atgaggagag accagggaga
301 gaatgggctc tctctctctc tcaactcccca accgagtaag tggtaaaaaa
351 ggttttctg gattacaatt ttggtgttac agaattggaa aaaaatattt
401 ttggggctcc cccctcagtt ta (SEQ ID NO: 8) --

Please amend the captioned paragraph beginning on line 1 of page 14 as follows:

-- SEQUENCE 9 (199.Seq)

1 ctagcaaaaa cccccccaca agttatgaaa acaacggctt aatatagtaa
51 tgtgtgtgtg tgtgtgtgtg tgttgacac cacagtttct tctgatactc
101 aaacctctct ctttctctac agggggcccc cataacacag cggtgagat
151 gtgtgacggg aaggcgtggc cttttacaca tttgtggtat ggtctgccaa
201 ggccccctat tgccccccac aactacggag atacactagg ggcgacccgc
251 aggcgcgcga ccccagggtg gggccccgag (SEQ ID NO: 9) --

Please amend the captioned paragraph beginning on line 8 of page 14 as follows:

-- SEQUENCE 10 (204.Seq)

1 ctttaggagg ttctctcgag taagcttttt ggatttcttt ggttcccaag
51 catcacatgg tacaggcagt cacacacaca cacatacaca cacacacaca
101 cacacacaca cactctctct cccacaatac ataccgagag gggggagaga
151 cactctctct ccctctctat agggggagcc ccacagagct ggctctgttg
201 tctctctcca ccggacatac agtggagcac atctcacact tctgtctcta

251 tctctccctg cccctgtgac atccatctct cttcacacaa tctcaccag
301 gatcttagcg ctagagaccc cctgtccttc ttctctggg gaaattttt
351 gtggataaga gacaccgat atattggtgt gggggagAAC atcttgtag
401 gtctctgttg tgccatccca acaggaattt ttatctccc cacaattaga
451 gccccctct caagagtgtg tgagggtt (SEQ ID NO: 10) --

Please amend the captioned paragraph beginning on line 1 of page 15 as follows:

-- **SEQUENCE 11 (235.Seq)**

1 gatcacagat gtatgtattt tttacatag gatagaaat ggacaatagg
51 aaataagaca gtacagctac taagaaagaa cccacattta cacacacaca
101 cacacacaca cacacacaca agtgtttaat ccgtgcaca gcattgtgga
151 catttttaca caagagagac acactctaca gtttgcgcc agctctag (SEQ ID NO: 11) --

Please amend the captioned paragraph beginning on line 6 of page 15 as follows:

-- **SEQUENCE 12 (249.Seq)**

1 gatcattctt ctgtttccca ttctaattga attctccaca cacacacaca
51 cacacacaca cacacactct tctttctct gacatggaaa aatctcccc
101 acaccccggtg acactgattt ctctccctct cccaacact gtgagcaaga
151 ggagtttatt ttgtgtgtgt cactcttcca gggagagaga gatc (SEQ ID NO: 12) --

Please amend the captioned paragraph beginning on line 11 of page 15 as follows:

-- **SEQUENCE 13 (258.Seq)**

1 ctaggcacg gttgggaggt ggtgagtaat tacttgtctg acattagtcc

51 tgtaacattg ggtgtgtgtg tgtgtgtgtg tgtgtattcc ccttggggaat
101 tggttttctc aaccacaagt tcttcttttt ttttttctc ccccctttc
151 ttctgaaaat aagtacttgg ggggtttccg ccccccccg taaataaaat (SEQ ID NO: 13) --

Please amend the captioned paragraph beginning on line 16 of page 15 as follows:

-- **SEQUENCE 14 (290.Seq)**

1 ctagtggtc ccaagcaaca catagccaga caacacacac acacacacac
51 acacacacac acacacacac acacacactc ctctccccac aatacatccc
101 gagagggggg agagacactc tctctccctc tctatagcgg gagccccaca
151 gagctggctc tgctgtctct ctacaccgga catacagtgg agcacatctc
201 acattcgtgt ctctatctct cctgcccct ggtgacatac atctctcttc
251 acacatctca ccaggtctga gcgctagagt ctctgtctt ctctctgcgc
301 aatatttgat atagagacat ctgatatatt gtgtgtggga gacatcttgt
351 gagtctctgt gtgcatccca gaggattttt atctccccac actag (SEQ ID NO: 14) --

Please amend the captioned paragraph beginning on line 6 of page 16 as follows:

-- **SEQUENCE 15 (309.Seq)**

1 gatccatgaa aactttccga gttgtattgt ctagtgaaa acacacacaa
51 acacacacac acacacacac acacaacagg gagatgagtc ttgcaagaga
101 ataggggaga gttatgtcac caagtctggt gaggtatata gcgtataggg
151 agccaacatg tcagacatct gatgtgctaa gattaacatt ttattttatt
201 taatgtgtga gatctcatat agcggctctt cttatatatg acgtctcgca
251 atgtctcttt atgtgtgtta ttctctgagc ccttgggaga tatctgtcat
301 cagagagaag agacatacac atacaggggt tatatatttt ctccctgtgt

351 gtggagatgg aggggtatfff ggacaagctc aacactcatt ggctcccaga

401 gagagaaaag gagcaactgt tgcacccggg gctctgtagc tgggatc (SEQ ID NO: 15) --

Please amend the captioned paragraph beginning on line 15 of page 16 as follows:

-- SEQUENCE 16 (341.Seq)

1 caattgggta catctacctg gtaccccacc cgggtggaaa atcgcattggg

51 cccgcggcgg ttctaggaag tactctcgag aagcttttgg gttctttggg

101 tccaagcag cacatggaca ggcaatcaca cacacacaca cacacacaca

151 cacacacaca cacacacaca ctctctccc cacaatacat ccgagaggg

201 gggagagtca ctctctctcc ctctctatag ggggcgcccc taagagtgg

251 ctctgttgc tatctacacc gcacatacaa tggagcacia ctacactag (SEQ ID NO: 16) --

Please amend the captioned paragraph beginning on line 2 of page 17 as follows:

-- SEQUENCE 17 (398.Seq)

1 gatcaaagca tggaggtcat gccaggcact gaacaaaatg gtagagagtg

51 attctatgac tgactaagac ctcatgcaac aacaagtga gagtcacaac

101 tgcaaacaga agtacaactt agcaaatcct atttcagga aacactaaac

151 cgtaatactt gcacgatttt ttcttaata cagtaataat tcttttagaa

201 ttggatata tcttttaaga tacatatttg tctaaatacc aaggcaggat

251 atgagcataa aatagctaag gttagctatg gtgttatatt taagaagacc

301 acagagcaat aggagcatac tttcttggg gtagaagggg cccttaaagg

351 tcacctag (SEQ ID NO: 17) --

Please amend the captioned paragraph beginning on line 11 of page 17 as follows:

-- **SEQUENCE 18 (420.Seq)**

1 ctagccacat cctataactc cactccacct ttaatcctga ttctgtgtc
51 tcttctctaa cctctatggc ctttctctaa agttccccaa tatcaacaat
101 ccttttcccc actgggacct ccagtttatt gattctacca tgtcactatc
151 catggtcaac cacttgttgt attataggat gtcgcgtgtg tgtgtgtgtg
201 tgtgtgcatg tgtgtgtgct tgggtgtcag agagttccaa tctgggggac
251 ctatgggttg taaacaacag gtctcttgcc aaggaagat (SEQ ID NO: 18) --

Please amend the captioned paragraph beginning on line 18 of page 17 as follows:

-- **SEQUENCE 19 (435.Seq)**

1 ctagegctcg tgcccctgca gttcgacact cagtggctcc tccacacaca
51 cacacacaca cacatcaata tatatataga tagatagata gatagaggag
101 caatataagt ggcttctcta ttccagcat gttttgaaga gcataaactc
151 aacagagtat atataaatct gatgtgacct atgtcatctg ctacagcatg
201 agagggggta gtgac (SEQ ID NO: 19) --

IN THE CLAIMS:

Please amend claim 1 as shown below:

1. (Amended) An isolated Z-chromosomal [marker] DNA selected from the group consisting of Sequence 1 (43.Seq) (SEQ ID NO: 1), Sequence 2 (71.Seq) (SEQ ID NO: 2), Sequence 3 (80.Seq) (SEQ ID NO: 3), Sequence 4 (81.Seq) (SEQ ID NO: 4), Sequence 5 (131.Seq) (SEQ ID NO: 5), Sequence 6 (147.Seq) (SEQ ID NO: 6), Sequence 7 (166.Seq) (SEQ ID NO: 7), Sequence 8 (196.Seq) (SEQ ID NO: 8), Sequence 9 (199.Seq) (SEQ ID

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NO: 9), Sequence 10 (204.Seq) (SEQ ID NO: 10), Sequence 11 (235.Seq) (SEQ ID NO: 11),
Sequence 12 (249.Seq) (SEQ ID NO: 12), Sequence 13 (258.Seq) (SEQ ID NO: 13),
Sequence 14 (290.Seq) (SEQ ID NO: 14), Sequence 15 (309.Seq) (SEQ ID NO: 15),
Sequence 16 (341.Seq) (SEQ ID NO: 16), Sequence 17 (398.Seq) (SEQ ID NO: 17),
Sequence 18 (420.Seq) (SEQ ID NO: 18), and Sequence 19 (435.Seq) (SEQ ID NO: 19).